brief communication

Hypopigmentation of the skin due to imatinib mesylate in patients with chronic myeloid leukemia

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BACKGROUND: Hypopigmentation is an infrequently reported adverse effect of imatinib mesylate (IM) in chronic myeloid leukemia (CML), but there are no reports from Arab or Saudi patients. Thus, we assessed the frequency and impact of hypopigmentation in patients with chronic myeloid leukemia (CML) taking IM in our institution in Riyadh.

PATIENTS AND METHODS: We studied 24 adult CML patients taking IM and followed from March to June 2008. Telephonic interviews with all the CML patients taking IM were conducted and case notes were reviewed. Findings were confirmed on a subsequent clinic visit by a physician. Demographic features, disease status, response to IM, presence and severity of skin changes and impact of these changes on the patients and the disease were noted.

RESULTS: Eight (33%) patients (6 males, 2 females) developed hypopigmentation due to IM. All patients had newly diagnosed, chronic phase CML and received 400 mg IM daily. The median age of the affected group was 37 years (range 18-54 years). Hypopigmentation developed during the first 3 months of treatment in 5 patients and 6 months or later in 3 patients. It was generalized in 7 patients and involved the hands and face in one patient. No photosensitivity was reported and none had other significant side effects.

CONCLUSION: Hypopigmentation of the skin can develop in about one third of CML patients taking IM. Physicians taking care of CML patients should be aware of this and patients need to be warned before commencing IM, particularly in dark-skinned patients.

Imatinib mesylate (IM) (Glivec; Novartis, Basel, Switzerland), a tyrosine kinase inhibitor (TKI), has become the standard of care for chronic myeloid leukemia (CML).[1,2] IM targets BCR-ABL protein, c-kit and platelet-derived growth factor receptor. IM is well tolerated and has a favorable safety profile.[2] Common side effects of IM include gastrointestinal disturbances, fluid retention, skin rashes and myelosuppression. Hypopigmentation is an infrequently reported adverse effect of IM in CML patients and has been reported in small series and case reports, but there are no reports from Arab or Saudi patients.

Hypopigmentation of the skin due to IM has been reported motly in black patients,[3,4] but there are reports of skin lightening in Indian patients as well as occasionally in whites.[5,6] It was described in an unusually high percentage (65%) of Malaysian (mostly ethnically Chinese) CML patients taking IM.[7] All of these patients had accelerated phase or interferon-resistant disease. These patients had received hydroxyurea previously, which may have caused skin pigmentation and made skin lightening more noticeable subsequently. Sharma et al also reported a variable degree of skin lightening in 22 of 26 Indian patients and attributed this to the darker skin complexion of their patient population.[5]

IM-induced skin hypopigmentation may have different patterns and may be diffuse or localized to certain parts of the body; usually exposed areas or vitiligo like and patchy.[8,9] The frequency and pattern of skin involvement appears to be variable in different reports and may have a genetic basis.[5,7] This unusual side effect may have important social and psychological impacts on patients and needs to be studied in detail in different populations. We describe our experience

with this phenomenon in Saudi patients with CML treated with IM.

PATIENTS AND METHODS

Patient notes and physician records on CML patients treated with IM, followed at King Khalid University Hospital, Riyadh, were reviewed. In addition, telephonic interviews with all the CML patients taking IM were conducted from March to June 2008. All patients gave informed consent. Patients were asked whether any skin lightening was noticed by the patient or the family. If the skin changes were noted, details and pattern of the hypopigmentation, time of onset and duration after start of IM treatment, aggravating factors like sunlight, presence of photosensitivity and any further changes in the pigmentation level, were inquired about. These findings were confirmed and documented by a physician during subsequent clinic visits. It was not possible to obtain photographs of the patients before and after the IM treatment. Patients were not taking any other medication known to be associated with pigment changes in the skin. One of the married female patients did not become pregnant since the start of IM treatment until the last follow-up. Disease status (phase) at the time of diagnosis and at the start of therapy, dose of IM, follow-up time and cytogenetic responses were recorded from the notes. Patients were considered to have a major cytogenetic response if the metaphase analysis of bone marrow showed less than 35% Philadelphia positive cells. The social impact of the skin change and the effect on the patient's life was also asked about. Skin biopsies were not done in any of our patients as they were considered unjustified and did not contribute to patient management.

RESULTS

Twenty-four adult patients receiving IM for CML were evaluated. Eight (33%) patients developed hypopigmentation of the skin, including 6 males and 2 females. The median age of the affected group was 37 years (range 18-54 years) and the median follow-up from the start of IM treatment was 15.5 months (range 8-30 months). All of these patients were in chronic phase CML at the time of diagnosis and all received IM, 400 mg daily. Seven patients had diffuse skin involvement with changes more prominent on the face and hands in two of these patients. One patient had skin changes confined mainly to the face and hands. The majority of the patients described the skin changes as moderate, or mild to moderate. Five patients (62.5%) developed observable skin changes during the first three months of therapy while 3 patients (37.5%) noticed the changes at 6 months or later. Hypopigmentation was persistent, although some patients reported fluctuations in the skin color. No photosensitivity was reported and patients noticed no changes in the skin related to exposure to the sun, except one patient. There were no other significant side effects of IM in any of these patients. All of the patients responded to IM with hematological response and seven achieved major cytogenetic responses (MCR). One patient did not achieve MCR after one year of therapy and shifted to a second-line TKI. This patient had reversal of skin lightening after stopping IM. The social impact on the lives of the patients was mostly positive or neutral. Three patients were happy (including 2 female patients) while the rest of the patients reported being indifferent to the changes. None of the patients reported embarrassment or depression due to the skin changes. Patient characteristics and results are given in Table 1.

DISCUSSION

In the 5-year follow-up of the International Randomized Study of Interferon (IRIS), skin involvement in the IM group occurred in 40% of patients.[10] In the original IRIS trial, these adverse events were reported to be skin rashes (most common), pruritus, alopecia and increased sweating.11 Hypopigmentation was not reported as a separate adverse event in these trials.

Hypopigmentation is more readily noticeable in patients with darker skin. As the majority of patients in the IM trials were white, this adverse effect was not observed frequently except in a few patients of African origin. Nevertheless it has been reported in a few white patients.[6,9] In a report from Malaysia, Leong et al reported the development of skin hypopigmentation in 65% of their CML patients treated with IM.[7] Almost all of these patients were ethnically Chinese and had interferon-resistant or accelerated phase disease. This appears to be an unusually high incidence of this phenomenon, but Sharma et al reported similar results in Indian patients.[5]

We report our experience in eight CML patients treated with IM who developed skin hypopigmentation. All of our patients were in chronic phase at the time of diagnosis and received the standard dose of IM (400 mg daily) and did not experience other notable toxicity. Tsao et al reported significant additional imatinib toxicity in their patients, which can possibly be explained by the higher doses these patients received; 600 mg in 4 patients and 800 mg in one patient.[3]

Hypopigmentation is more likely to be observed in dark-skinned patients but we observed it in some patients with fair skin as well. The majority of our patients

Table 1. Patient characteristics and results.

No.	Age (years)	Gender	Time skin changes noted after start of therapy	Dose of imatinib (mg)	Severity of skin changes (as perceived by the patients)	Pattern of skin involvement	MCR	Follow-up (months)
1	26	M	1 M	400	Moderate	Diffuse and generalized (more prominent hands and feet)	No	12
2	37	M	3 M	400	Mild	Diffuse and generalized	Yes	10
3	25	F	2M	400	Moderate	Diffuse and generalized	Yes	8
4	18	M	2M	400	Moderate	Diffuse and generalized	Yes	15
5	38	M	6M	500	Moderate	Hands and face	Yes	27
6	54	M	6M	400	Mild-moderate	Diffuse and generalized	Yes	16
7	37	M	3 M	400	Moderate-severe	Diffuse and generalized	Yes	16
8	42	F	>6 month	400	Mild	Diffuse and generalized	Yes	30

MCR: major cytogenetic response; yrs: years

had generalized skin lightening except one patient who developed changes mainly on the face and hands. One of our patients who discontinued IM due to poor response had reversal of skin lightening. The skin changes have been reported to be reversible on discontinuation of IM indicating that this effect is not permanent.[3]

Pathogenesis of skin hypopigmentation by IM is not fully understood, but involves the blockade of the c-kit (KIT) receptor tyrosine kinase pathway. Receptor c-kit and its ligand stem cell factor (SCF) have an important role in the homeostasis and in the development and survival of melanocytes. C-kit and stem cell factor also have an important role in migration of the melanoblasts from the neural tube to the skin during embryogenesis.[12,13] This is supported by the observation that human mutations in the encoded tyrosine kinase region of c-kit cause piebaldism, an autosomal dominant disorder characterized by white hair and hypopigmented skin patches on the forehead, torso, and extremities.[14] In addition, murine models with human xenograft skin were subjected to c-kit inhibitory antibody (K44.2), which led to melanocyte loss and a decrease in differentiation antigens and melanocyte dendritic processes. Prolonged c-kit inhibition led to melanocyte apoptosis.[15,16] These findings provide evidence of a critical role for SCF/KIT in the homeostasis and survival of human melanocytes.

IM inhibits c-kit and by doing so seems to inhibit melanocytes, which can very well explain the development of hypopigmentation. Why some patients develop hypopigmentation, while others have no effect on their skin and whether those patients who do not develop skin lightening may be at a higher risk of relapse are unresolved questions. The answer to the first question is not known, but may be related to the variable inhibition of relevant tyrosine kinase. Regarding the second question, there is no evidence to suggest that there are any differences in disease response in two groups of patients.

Currently IM is recommended to be continued indefinitely in responding patients.[1] For this reason the number of patients taking IM will continue to rise. In the future, this is likely to increase the number of patients who develop skin hypopigmentation. There are important psycho-social implications of this phenomenon. It may not be acceptable to patients from certain racial backgrounds and may cause social embarrassment. On the contrary, whitening of the skin may be welcome in certain communities. This may render IM for potential abuse. Particularly patients with dark skin should be warned of this adverse effect before commencing IM treatment. In our opinion, if hypopigmentation of the skin causes significant disturbance to the patient, it may be an indication to switch to a second line TKI.

This skin lightening effect of IM may have at least one therapeutic potential. Patients with vitiligo and patchy hypopigmentation may benefit .[17] A generalized

hypopigmentation would be useful in these patients to make the patchy areas less conspicuous, particularly on the exposed parts of the body. As stopping of IM usually reverses the hypopigmentation, this treatment will need to be taken for long periods. The cost of the drug and long-term side effects of IM would be of concern in this group of patients. Alternatively, local application of an IM skin preparation may be useful on the exposed parts of the body and is likely to have less side effects. Until trials of systemic or local IM use are conducted in these patients, IM can not be recommended for this purpose.

In summary, hypopigmentation of the skin can develop in a significant number of patients taking IM for CML. Physicians taking care of CML patients should be aware of this, and patients should be warned about this adverse effect before commencing IM, particularly in dark-skinned patients.

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